The opinion in support of the decision being entered today is *not* binding precedent of the Board.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte WENDA C. CARLYLE, SHEILA J. KELLY, and MATTHEW F. OGLE

Appeal 2007-2321
Application 09/014,087
Technology Center 3700

Decided: September 20, 2007

Before TONI R. SCHEINER, DEMETRA J. MILLS, and NANCY J. LINCK, *Administrative Patent Judges*.

LINCK, *Administrative Patent Judge*.

DECISION ON APPEAL

This is a 35 U.S.C. § 134 appeal in the above-referenced case.[1]

We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

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[1] The application was filed January 27, 1998. The real party in interest is St. Jude Medical, Inc.

STATEMENT OF THE CASE

The field of the invention is "prostheses having components that have been modified with a polypeptide growth factor" (Specification ("Spec.") 1).

According to the Specification, prior art prostheses have been "constructed from natural materials such as tissue, synthetic materials or a combination thereof" (Spec. 1). Furthermore, prosthetic heart valves have been made from porcine heart valves and bovine pericardium but such valves are "limited by a tendency to fail beginning about seven years following implantation" (Spec. 2).

"Calcification . . . appears to be a major cause of degeneration," and "evidence suggests that glutaraldehyde fixation can contribute to calcification and mechanical degradation" (*id.*)[2]. Further, "since nonviable cells can be sites for calcium deposition, various processes have been developed to remove nonviable cells while leaving the extracellular matrix intact. Intact tissue with viable cells has natural protection against calcification." (Spec. 2.)

"Another major disadvantage of tissue based prostheses is the failure of such devices to be self-maintaining. Long term durability is affected by the ability of viable cells to populate the implanted tissue and to carry out maintenance functions. The importance of viable cells has been studied in the context of allograft transplants . . . " (Spec. 3).

Appellants join a "polypeptide growth factor," for example VEGF, with a "tissue substrate or a synthetic substrate to promote population of the

[2] Fixation by crosslinking "provides mechanical stabilization" and "removes antigenic sites that could result in a patient's rejection of the prosthesis" (Spec. 8). "Glutaraldehyde typically is used for fixation" (*id.*).

substrate with viable cells" (Spec. 3). According to Appellants, with "crosslinked tissue, associated VEGF alleviates at least some of the cellular toxicity resulting from glutaraldehyde crosslinking" (*id.*). Further, according to Appellants, a "substrate modified with VEGF provides for affiliation of viable endothelial cells with the substrate to improve the performance of the substrate as a prosthesis," such as long term durability and reduction in the incidence of infection (*id.* at 3-4).

The Claims

The claimed subject matter is reflected in independent claims 1, 14, and 25:

> 1. A prosthesis for a human patient comprising allograft or xenograft tissue having a polypeptide growth factor associated therewith by a biologic adhesive, antibody-antigen associations, specific binding protein-receptor associations or enzyme substrate associations, said polypeptide growth factor being effective to stimulate the affiliation of viable cells with said tissue.
>
> 14. A prosthetic heart valve comprising a substrate with associated VEGF, wherein said VEGF is associated with the substrate by direct attachment, a biologic adhesive, antibody-antigen associations, specific binding protein-receptor associations or enzyme-substrate associations, the prosthesis having a valve structure, said polypeptide growth factors being effective to stimulate the affiliation of viable cells with said substrate.
>
> 25. A prosthesis comprising crosslinked natural tissue having an exogenous polypeptide growth factor associated herewith.

We focus our analyses on these claims, as the remaining claims have not been separately argued.

The Issues

The Examiner has rejected claims 1, 2, 4-11, 14, 15, and 21-28 based on the following references:

Cahalan	U.S. 5,308,641	May 3, 1994
Bayne	EP 0476983	Mar. 25, 1992
Wadström	U.S. 5,631,011	May 20, 1997
Carpentier	U.S. 4,648,881	Mar. 10, 1987

The specific issues raised by the Examiner's rejections are as follows:

A. Whether claims 25 and 28 are anticipated under 35 U.S.C. §102(b) based on Cahalan;

B. Whether claims 25 and 26 are anticipated under 35 U.S.C. §102(b) or, alternatively, would have been obvious under 35 U.S.C. §103(a) based on Bayne;

C. Whether claims 1-2, 4-5, and 9-11 would have been obvious under 35 U.S.C. § 103(a) based on Bayne and Wadström; and

D. Whether claims 6-8, 14, 15, 21-24, 27, and 28 would have been obvious under 35 U.S.C. § 103(a) based on Bayne, Wadström, and Carpentier.

The Examiner has also raised the issue of obviousness-type double patenting with respect to claims 1, 2, 9, 14, and 21 in view of claims 1, 8, 10, 13, 15, 34, 35, and 38-40 of application 09/186,810 (Answer[3] 3-4).

DISCUSSION

A. Anticipation of Claims 25 and 28

Appellants argue Cahalan does not anticipate these claims because Cahalan does not disclose (1) "crosslinking natural tissue" or (2) "growth

[3] "Answer" refers to the Examiner's Answer (mailed Apr. 5, 2006).

factor associated therewith." (Appeal Br. 4-8; Reply Br. 4-6.)[4] According to Appellants, only Cahalan's polyalkyimine spacer is crosslinked, not the natural tissue, and Cahalan's growth factor is attached to the spacer rather than the natural tissue (*id.*).

With respect to Appellants' first argument, the Examiner responds: "the crosslinking treatment would . . . inherently crosslink the tissue protein to some extent" (Answer 8).

With respect to Appellants' second argument, according to the Examiner, "the term 'associated' does not mean bonded or attached in any manner' but "can include materials that are merely next to each other" (*id.*).

Findings of Fact[5]

1. Prostheses employing crosslinked natural tissue were well known in the art at the time the subject invention was made (*see* Spec. 8; Carpentier *passim*).

2. The terms "fixation" (or "fixing") and "crosslinking" were used interchangeably by those skilled in the art at the time the subject invention was made (*see id.*; Answer 5).

3. At that time, glutaraldehyde was a commonly used fixation or crosslinking agent (*id.*).

4. It was known in the relevant art that fixing or crosslinking biological tissue "provides mechanical stabilization" (Spec. 8; *see also* Carpentier, col. 1, ll. 6-21) and other advantages (*id.*).

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[4] "Appeal Br." and "Reply Br." refer to the Amended Brief and Reply Brief, respectively (both received June 7, 2006).

[5] Findings of Fact are abbreviated "FF."

5. Claim 25 is written in "comprising" format and thus does not exclude other elements.

6. Claim 25 requires "crosslinked natural tissue" but does not require any specific degree of crosslinking.

7. The "natural tissue" of claim 25, once crosslinked, is modified and no longer in its naturally occurring form, and thus could be considered artificial or synthetic.

8. The term "crosslinked" is not defined in the Specification (*see* Spec. *passim*) and thus must be given its broadest reasonable interpretation, and includes varying degrees of crosslinking (FF 6).

9. The term "associated therewith" is not defined in the Specification but includes "hydrogen bonding, van der Waals interactions" (Spec. 14, 12-13) and can involve a linker, with "the linker . . . covalently bound to the tissue and the VEGF . . . associated with the linker" (Spec. 15, ll. 17-23).

10. Thus, the broadest reasonable interpretation of "associated therewith" does not require attaching the VEGF directly to the tissue (FF 9).

11. Cahalan discloses using a "spacer" to attach biomolecules, such as growth factors, to previously known solid surfaces, including natural tissue (col. 1, ll. 37-46; col. 4, ll. 16-33) but does not expressly describe the natural tissue as either crosslinked or uncrosslinked.

12. Cahalan applies a polyalkylimine to the solid surface with a crosslinking agent, which can be glutaraldehyde (col. 4, ll. 58-66).

13. "*Preferably*, the crosslinking agent used to crosslink the polyalkylimine is applied in dilute solution [*preferably* 0.0005M to 0.005M] to accomplish light crosslinking" (col. 4, l. 66 to col. 5, l. 6 (emphasis

added) but Calahan discloses higher concentrations, such as 0.05 M aldehyde (col. 5, ll. 3-5).

14. According to Cahalan, the "time required to complete the light crosslinking is typically just a few minutes" (col. 5, ll. 9-10).

15. However, when Cahalan wants to crosslink the spacer and attach the spacer simultaneously to the surface, Cahalan teaches "the aldehyde concentration and/or reaction time used may be greater in order to ensure the presence of adequate aldehyde functionality on the activated surface" (col. 5, ll. 20-25).

16. Cahalan's crosslinking treatment with glutaraldehyde would be expected to inherently crosslink the tissue, at least to some extent, particularly when Cahalan simultaneously crosslinks the spacer and binds the spacer to the surface (FF 12-15; Answer 8).

17. Finally, based on our interpretation of "associated therewith," Cahalan's attachment of growth factors to spacers which in turn are attached to a natural tissue provides growth factors "associated" with the tissue, just as Appellants' attachment of growth factors through linkers does (FF 9, 10).

18. Claim 25 is prima facie anticipated by Cahalan (FF 5-17).

19. The evidence submitted by Appellants (Exhibit A) is not sufficient to overcome the Examiner's prima facie case in that (1) unlike Appellants' claims, the reference relied on by Appellants is limited to crosslinked collagen fibers which are particularly difficult to crosslink (Biotechnology, Vol. III, Collagen 2, 3, 13 (Nimni, Ed.) (1988); and (2) the reference discloses some degree of reaction in a matter of minutes for 0.04 M glutaraldehyde (*id.* at 13, FIG. 8), a concentration less than that taught by Cahalan (FF 13).

Discussion of the Patentability of Claim 25 Over Cahalan

The Examiner found Cahalan taught each limitation of claim 25, including the "crosslinked natural tissue" and "associated therewith" limitations, either expressly or inherently. We agree. With respect to these disputed terms, when given their broadest reasonable interpretation, they encompass Cahalan's teachings, either expressly or inherently (FF 5-17).

While admitting that "with enough time and at adequate concentrations [both unspecified], glutaraldehyde will fix a tissue," Appellants argue Cahalan's concentrations and times are not sufficient to crosslink Cahalan's natural tissue (Appeal Br. 5-7). We disagree. The record, including that cited by Appellants (FF 19), establishes a prima facie case that Cahalan's natural tissue would be inherently "crosslinked," at least to a degree sufficient to satisfy claim 25 (FF 6, 8, 12-16) and shift the burden to Appellants to establish otherwise.

> Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. . . . Whether the rejection is based on `inherency' under 35 U.S.C. § 102, on `prima facie obviousness' under 35 U.S.C. § 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products.

In re Best, 562 F.2d 1252, 1255 (CCPA 1977).

Finally, Appellants argue Cahalan's "growth factor . . . is not next to the crosslinked natural tissue" but rather is "associated with the spacer which

separates and is positioned between the . . . growth factor and the substrate" (Reply Br. 6). We disagree based on our findings above (FF 9, 10, 17). Thus, we find Cahalan anticipates claim 25.[6]

B. The Rejection of Claims 25 and 26 Under § 102(b) or § 103(a)

The Examiner rejected claims 25 and 26 based on Bayne, finding "the crosslinked natural tissue . . . is the fixed umbilical cord vein" and the "growth factor . . . is the VEGF II . . . coated onto the tubular support prior to implantation" (Answer 5 (citing "in particular," Bayne at 8, ll. 20-23)). According to the Examiner, "the tubular supports coated with VEGF II include fixed umbilical cord vein" (*id.* at 5).

Alternatively, the Examiner found "it would have been clearly obvious to use umbilical cord vein as the tubular support since it is used as an implant in another procedure; it would bring the desired features of tissue properties to the implant site" (Answer 5-6).

Appellants argue Bayne does not disclose "VEGF II growth factor [applied] to a surface of a fixed umbilical cord vein" (Appeal Br. 9) but rather teaches "two separate procedures for preparing a natural tissue and an artificial implant," improperly linked by the Examiner (Reply Br. 7). According to Appellants, their position is supported by Bayne's terminology which "clearly indicates that Bayne considered a tubular support to be an artificial support and a natural tissue to be something other than an artificial tubular support, otherwise common terminology would have been used

[6] While there is no § 103 rejection based on Cahalan, we noted that it would have been obvious to use crosslinked natural tissue in Cahalan's prostheses, as such use was well known in the relevant art (FF 1-4).

throughout the paragraph in question" (Reply Br. 7-8 (referring to Bayne at 8, ll. 14-23)).

Findings of Fact

20. Bayne discloses that VEGF II is useful "to stimulate endothelial cells for . . . the production of artificial blood vessels" (Bayne at 3, ll. 33-34).

21. Bayne further discloses his "growth factors . . . are useful for the coverage of artificial blood vessels with vascular endothelial cells" (*id.* at 8, ll. 14-15).

22. One example of a useful artificial blood vessel is "fixed umbilical vein" (*id.* at 8, l. 19).

23. Bayne discloses:

> The novel growth factors of this invention are useful for the coverage of *artificial blood vessels* with vascular endothelial cells. Vascular endothelial cells . . . would be grown in culture in the presence of VEGF II . . . . After growth of adequate numbers of endothelial cells in culture to cover a *synthetic polymeric blood vessel* the cells would be plated on the inside surface of the *vessel, such as fixed umbilical vein*, which is then implanted in the patient. Alternatively, *tubular supports* are coated *in vitro* with VEGF II prior to implantation into a patient. Following implantation endothelial cells migrate into and grow on the *artificial surface*. Prior coating of the *artificial vessel* . . . with proteins such as fibrin . . . would be performed to enhance attachment of the cells to the *artificial surface*. [Bayne, at 8, ll. 14-23 (emphasis added).]

24. Based on the language of this paragraph as a whole and particularly on the language "a synthetic polymeric blood vessel . . . , such as fixed umbilical vein" (*id.*, ll. 17-19), (1) Bayne's use of the term "artificial blood vessels" in the first sentence refers to the following vessels

discussed in the same paragraph: "artificial blood vessels," "synthetic polymeric blood vessel," "fixed umbilical vein," "tubular supports," and "artificial vessel;" and (2) Bayne's use of the term "artificial surface" refers to the surface of each of these artificial blood vessels (FF 23; Bayne at 8, ll. 14-23).

25. Bayne's umbilical vein, *when fixed*, no longer is considered natural tissue but rather a "synthetic polymeric blood vessel" (FF 23, 24; Bayne at 8, ll. 17-19); this interpretation harmonizes the language of the sentence containing these terms (*id.*).

26. Thus, Bayne discloses a method of preparing a "prosthesis" (artificial blood vessels) "comprising crosslinked natural tissue" (fixed umbilical vein) having "an exogenous polypeptide growth factor" (VEGF II) "associated therewith" (coated on the vein) (FF 23-25); and, therefore, anticipates claim 25.

27. In any case, even if Bayne were not so read, the skilled artisan would have been motivated to use crosslinked natural tissue, such as fixed umbilical cord vein, because of its known advantages (FF 1-4) and would have had a reasonable expectation of success based on what was known in the art (*id.*).

Discussion of the Patentability of Claim 25 Over Bayne

Based on the above and the Examiner's findings, we find claim 25 is anticipated by Bayne (FF 20-26). Alternatively, we conclude claim 25 would have been obvious to one of ordinary skill in the art at the time Appellants' claimed invention was made (FF 1-4, 20-27). The difference between Bayne and the invention of claim 25 is, at most, the nature of the surface to which the VEGF II was applied. And the knowledge in the

relevant art at the relevant time included knowledge of alternative surface materials for prostheses and the advantages of crosslinked natural tissue (FF 1-4). Such knowledge would have been sufficient to bridge any gap between Appellants' claimed invention and the prior art teachings. Appellants did no more than combine well known elements, with known functions, to yield predictable results. *See KSR Int'l v. Teleflex Inc.*, 127 S. Ct. 1727, 1740 (2007).

C. The Patentability of Claims 1-2, 4-5, and 9-11 Under § 103(a)

The Examiner rejected these claims based on Bayne and Wadström. Instead of requiring "crosslinked natural tissue," claim 1 requires "allograft or xenograft tissue" and further requires the growth factor to be "associated therewith by a biologic adhesive." The biologic adhesive can be a commercially available fibrin glue (Spec. 13).

Appellants argue these claims would not have been obvious over Bayne and Wadström because (1) allograft and xenograft tissues are not disclosed by either reference, and (2) Bayne "does not disclose coating fibrin and growth factor on fixed umbilical cord vein" (Appeal Br. 14). Rather, according to Appellants, Bayne discloses "coating fibrin and growth factor on an artificial vessel" (*id.*). Appellants do not dispute the Examiner's finding that fibrin is "considered to be a biological adhesive in the art," as disclosed by Wadström (Answer 9).

While admitting the references do not expressly disclose allograft and xenograft tissues, the Examiner found such tissues encompass "virtually all sources of tissue" and concluded "the use of one or the other would not

patentably distinguish the claimed invention . . . absent some showing of unexpected and unobvious results" (Answer 10).

With respect to Appellants' argument that Bayne does not disclose coating fibrin and growth factor on fixed umbilical cord vein, the Examiner relies on his previous finding that "a combination of . . . fibrin, and growth factor (VEGF II) would have been at least obvious in view of Bayne alone" (Answer 6 & Bayne at 8, ll. 20-23 (Answer 5)).

Findings of Fact

28. "[F]ibrin is considered to be a biological adhesive in the art" (Answer 9 (citing Wadström)).

29. Allograft and xenograft tissue encompass "virtually all sources" of natural tissue (Answer 10 (undisputed by Appellants)).

30. Thus, one skilled in the art would have envisioned allograft and xenograft tissue when presented with the genus "natural tissue" (FF 29).

31. Bayne discloses coating fixed umbilical cord vein with growth factor and fibrin "to enhance attachment of the cells to the artificial surface," including the surface of fixed umbilical vein (FF 23; Bayne at 8, ll. 21-23).

32. Alternatively, the skilled artisan would have been motivated to coat crosslinked natural tissue with fibrin, along with growth factor, "to enhance attachment" of cells to the crosslinked natural tissue (FF 31) and would have had a reasonable expectation of success, based on Bayne's teachings.

Discussion of the Patentability of Claim 1

Based on the above and the Examiner's findings, we conclude claim 1 would have been obvious to an artisan of ordinary skill (FF 20-32). Appellants have merely associated a growth factor with surfaces well known

in the art (FF 1-4) using a biologic adhesive also known in the art (FF 28). Such a combination is merely a "predictable use of prior art elements according to their established functions." *KSR Int'l*, 127 S. Ct. at 1740.

Again, we reject Appellants' argument that Bayne does not disclose coating fibrin and growth factor on fixed umbilical cord vein, but instead on an artificial vessel, for the reasons given relating to the § 102 rejection of claim 25 based on Bayne (*see* FF 23-27). We also reject Appellants' argument that their claimed invention would not have been obvious because neither of the cited references expressly discloses "allograft or xenograft tissue" (*see* FF 29-30). Obviousness does not require express disclosure of every claim limitation but can be based upon what the prior art "fairly suggests." *In re Baird*, 16 F.3d 380, 383 (Fed. Cir. 1994). The express disclosure of natural tissue in the context of prostheses clearly would have suggested allograft or xenograft tissue to the skilled artisan.

D. The § 103(a) Rejection of Claims 6-8, 14, 15, 21-24, 27, and 28

These claims further define the types of prostheses and tissues used for the prostheses. With reference to claim 14, it is directed to a "prosthetic heart valve". The Examiner relied upon on Bayne, Wadström, and Carpentier to support this rejection (Answer 7).

Appellants do not dispute that Carpentier "discloses many different *natural* tissues that can be used as heart valve prostheses" (Reply Br. 9 (emphasis Appellants')). Rather, they again argue "the Examiner improperly modified the Bayne application to combine mutually exclusive methods of preparing a *natural* tissue . . . with the method for preparing an *artificial* vessel . . . as previously discussed above with respect to claims 1

and 25" (Reply Br. 9 (emphasis Appellants')). Thus, according to Appellants, the "combination of the Bayne application with the Carpentier patent would not provide a prosthetic heart valve comprising a substrate associated with VEGF as claimed in claim 14" (*id.*).

For the reasons given previously, we reject this argument (see pp. 10-12; FF 23-27). Thus, we conclude these claims would have been obvious to one of ordinary skill in the art based on Bayne, Wadström, and Carpentier.

The Examiner's Provisional Double-Patenting Rejection

Appellants do not dispute the propriety of the Examiner's double patenting rejection but rather state: "Applicants will consider filing a terminal disclaimer in the event that co-[p]ending application Serial No. 09/186,810 issues into a patent" (Appeal Br. 17). We disagree with Appellants' statement that this issue is "moot" (*id.*), and affirm the Examiner's provisional double-patenting rejection.

CONCLUSION

In summary, we affirm the following rejections: claim 25 under § 102 based on Cahalan; claim 25 under § 102(b), and alternatively under § 103(a), based on Bayne; claim 1 under § 103(a) based on Bayne and Wadström; and claim 14 under § 103(a) based on Bayne, Wadström, and Carpentier.

Pursuant to § 41.37(c)(1)(vii)(2006), we also affirm the rejection of claims 2, 4-11, 15, 21-24, and 26-28, as these claims were not argued separately.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1)(iv)(2006).

AFFIRMED

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